Supporting material

Experimental

General procedure for synthesis of 2: To a solution of **1** (10 mmol) in 5 mL of methanol was added 1 mL of HOAc, the solution was stirred at room temperature for 5 minutes, then the solvent was evaporated. The residue was dissolved in 15 mL of dry benzene and then 0.1mL of HOAc and 12 mmol of β-ketoester were added. The flask was attached to a water separator before the solution was heated to reflux to separate water. After the reaction was completed, the solution was cooled to room temperature and to this solution 10 mL of 20% K_2CO_3 solution was added. The organic phase was separated, the aqueous phase was extracted with CH_2Cl_2 for three times. The combined organic phase was dried and condensed, the residue was chromatographed to give the corresponding enamine. The enamine was dissolved in 10 mL of dry alcohol, to this solution was added 0.7g (30 mmol) of sodium, then the mixture was heated to reflux and the reflux was continued for 12 hours. After cooled to room temperature, 10 mL of saturated NH_4Cl solution was added, then the mixture was extracted with CH_2Cl_2 for five times, the combined organic phase was dried and condensed, the residue was chromotographed to give **2**.

(2*R*)-2,6-Dimethyl-4-oxo-1,2,3,4-tetrahydropyridine-5-carboxylic acid methyl ester 2a: 83%; $[\alpha]_D^{20}$ +320.1 (*c* 1.54, $CHCl_3$); IR(neat) 3246, 3084, 2969, 1683, 1624, 1574 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.59 (br s, 1H), 3.78 (m, 1H), 3.76 (s, 3H), 2.47 (dd, *J* = 15.8, 4.8 Hz, 1H), 2.36 (dd, *J* = 15.8, 12.4 Hz, 1H), 2.31 (s, 3H), 1.32 (d, *J* = 6.5 Hz, 3H); EIMS *m/z* 183 (M^+); Anal. Calcd. for $C_9H_{13}NO_3$ requires C: 59.00, H: 7.15, N: 7.64, found C: 59.05, H: 6.78, N: 7.24.

(2*S*)-2-Phenyl-6-methyl-4-oxo-1,2,3,4-tetrahydropyridine-5-carboxylic acid ethyl ester 2b: 81%; $[\alpha]_D^{11}$ +158.0 (*c* 1.0, $CHCl_3$); IR (neat) 3215, 3062, 1699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (m, 5H), 5.70 (br s, 1H), 4.68 (dd, *J* = 14.0, 5.8 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.73 (dd, *J* = 15.9, 14.0 Hz, 1H), 2.66 (dd, *J* = 15.9, 5.8 Hz, 1H), 2.33 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); EIMS *m/z* 259 (M^+); HRMS found *m/z* 259.1208 (M^+), $C_{15}H_{17}NO_3$ requires 259.1208.

(2*S*)-2-Phenyl-6-propyl-4-oxo-1,2,3,4-tetrahydropyridine-5-carboxylic acid ethyl ester 2c: 79%; $[\alpha]_D^{20}$ +116.2 (*c* 1.48, $CHCl_3$); IR (neat) 3244, 2976, 1692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 5H), 5.49 (br s, 1H), 4.72 (dd, *J* = 14.2, 4.8 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.65 (m, 4H), 1.68 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.02 (t, *J* = 7.0 Hz, 3H); EIMS *m/z* 287 (M^+); HRMS found *m/z* 287.1523, $C_{17}H_{21}NO_3$ requires 287.1524.

General procedure for synthesis of 3: To a solution of **2** (3 mmol) in 10 mL of methanol was added 10 mL of 25% aqueous NaOH, the mixture was heated to reflux and the refluxing was continued for 6 h. After the mixture was cooled to room temperature, 10 mL of saturated NH_4Cl solution was added. The solution was extracted with CH_2Cl_2 for five times, the combined organic phase was dried and condensed, the residue was chromatographed to give **3**.

(2*R*)-2,6-Dimethyl-1,2,3,4-tetrahydropyridine-4-one 3a: 79%; $[\alpha]_D^{16}$ +497.6 (*c* 0.54, $CHCl_3$); IR(neat) 3269, 1610, 1575, 1537 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.95 (br s, 1H), 4.94 (s, 1H), 3.77 (m, 1H), 2.35 (dd, *J* = 16.2, 5.3 Hz, 1H), 2.27 (dd, *J* = 16.2, 13.1 Hz, 1H), 1.98 (s, 3H), 1.31 (d, *J* = 6.5 Hz, 3H); EIMS *m/z* 125 (M^+); Anal. Calcd. for $C_7H_{11}NO$ requires C: 67.17, H: 8.86, N: 11.19, found C: 67.00, H: 8.89, N: 11.22.

(2*S*)-2-Phenyl-6-methyl-1,2,3,4-tetrahydropyridine-4-one 3b: 78%; $[\alpha]_D^{11}$ +173.2 (*c* 0.55, $CHCl_3$); IR (neat) 3219, 3033, 1610, 1577, 1529 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 5H), 5.01 (s, 1H), 4.98 (br s, 1H), 4.66 (dd, *J* = 14.8, 4.8 Hz, 1H), 2.63 (dd, *J* = 16.2, 14.8 Hz, 1H), 2.43 (dd, *J* = 16.2, 4.8 Hz, 1H), 2.00 (s, 3H); EIMS *m/z* 187 (M^+); HRMS found *m/z* 187.0994 (M^+), $C_{12}H_{14}NO$ requires 187.0991.

(2*S*)-2-Phenyl-6-propyl-1,2,3,4-tetrahydropyridine-4-one 3c: 77%; $[\alpha]_D^{20}$ +95.7 (*c* 0.7, $CHCl_3$); IR (neat) 3215, 3061, 2960, 1608, 1574, 1523 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 5H), 5.05 (s, 1H), 4.98 (br s, 1H), 4.70 (dd, *J* = 14.6, 4.8 Hz, 1H), 2.64 (dd, *J* = 16.1, 14.6 Hz, 1H), 2.45 (dd, *J* = 16.1, 4.8 Hz, 1H), 2.21 (m, 2H), 1.63 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H); EIMS *m/z* 215 (M^+); Anal. Calcd. for $C_{14}H_{17}NO$ requires C: 78.10, H: 7.95, N: 6.50, found C: 78.10, H: 7.95, N: 6.35.

General procedure for synthesis of 4: To a solution of **3** (1 mmol) in 10 mL of methanol was added 20 mg of 10%Pd/C, the mixture was stirred under H_2 (50 atm) at 50 ^oC for 24 h. After the catalyst was filtered off, the filtrate was condensed and the residue was chromatographed to give **4**.

(2*S*,4*R*,6*S*)- 2-Phenyl-6-methyl-4-piperidinol 4a: 95%; $[\alpha]_D^{11}$ –5.9 (*c* 0.8, CH_3OH); IR (neat) 3348, 2933, 2806 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H), 3.84 (m, 1H), 3.42 (dd, *J* = 11.5, 2.4 Hz, 1H), 2.90 (m, 1H), 2.15 (m, 1H), 2.01 (m, 1H), 1.49 (ddd, *J* = 11.4, 11.4, 11.4 Hz, 1H), 1.25 (ddd, *J* = 11.3, 11.3, 11.3 Hz, 1H), 1.19 (d, *J* = 6.3 Hz, 3H); EIMS *m/z* 191 (M^+); HRMS found *m/z* 191.1304 (M^+), $C_{12}H_{17}NO$ requires 191.1298.

(2*S*,4*R*,6*S*)- 2-Phenyl-6-propyl-4-piperidinol 4b: 95%; $[\alpha]_D^{20}$ +0.9 (*c* 1.2, CH_3OH); IR (neat) 3388, 2933, 2806 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H),

3.89 (m, 1H), 3.44 (dd, *J* = 11.6, 2.5 Hz, 1H), 2.88 (m, 1H), 2.18 (m, 1H), 2.05 (m, 1H), 1.70 (m, 3H), 1.45 (m, 2H), 1.25 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H); EIMS *m/z* 220 (M^+ + H^+); HRMS found *m/z* 176.1079(M^+-C_3H_7), $C_{11}H_{14}NO$ requires 176.1083.

(3*S*)-3-(*N*-phenylmethyl-*N*-((*R*)-1'-phenylethyl))-amino-dodecanoic acid ethyl ester 6. A solution of (*S*)-*N*-phenyl-(α)-methylbenzyl amine (3.5 g, 16.6 mmol) in 30 mL of dry THF was cooled to -78 ^oC, to this solution was added 8 mL of 2 M BuLi, the solution was stirred for 2 h, during which time the temperature rose to -20 ^oC. The temperature was cooled to -78 ^oC again, to this solution was added a solution of **5** (3 g, 13.3 mmol) in 5 mL of dry THF rapidly with vigorous stirring. The stirring was continued for 2 min, then 10 mL of saturated NH_4Cl solution was added. After the temperature rose to temperature, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (20 mL × 3). The combined organic phase was dried and condensed, the residue was chromotographed to give 4.6 g (79%) of **6**. $[\alpha]_D^{11}$ -4.6 (*c* 3.1, $CHCl_3$); IR (neat) 2928, 2855, 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7.50 (m, 10H), 4.03 (m, 2H), 3.85 (q, *J* = 7.0 Hz, 1H), 3.80 (d, J = 14.8 Hz, 1H), 3.55 (d, *J* = 14.8 Hz, 1H), 3.38 (m, 1H), 2.03 (m, 2H), 1.55 (m, 2H), 1.34 (d, *J* = 7.0 Hz, 3H), 1.27 (br s, 14H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H); EIMS *m/z* 438 (M^+ + H^+), HRMS found *m/z* 437.3278 (M^+), $C_{29}H_{43}NO_2$ requires 437.3262.

(2*S*)-2-Nonyl-6-methyl-4-oxo-1,2,3,4-tetrahydropyridine-5-carboxylic acid ethyl ester 7. To a solution of **6** 3.5g (8 mmol) in 15 mL of ethanol was added 0.4 g of 10% Pd-C, the mixture was stirred under H_2 (30 atm) at room temperature for 24 h, then the catalyst was filtered off. To the filtrate was added 2 mL of HOAc, the solution was stirred at room temperature for 5 min, then the solvent was evaporated. The residue was

dissolved in 25 mL of benzene, to this solution was added 0.1mL of HOAc and ethyl acetoacetate (1.2 g, 9.2 mmol), then the solution was heated to reflux to separate water. After the reaction was completed the mixture was cooled to room temperature and 5 mL of 20% K_2CO_3 solution was added, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL × 5). The combined organic phase was dried and condensed, the residue was chromatographed to give enamine. The enamine was dissolved in 20 mL of dry ethanol, to this solution was added sodium (0.55 g, 24 mmol), the mixture was heated to reflux and the reflux was continued for 12 h. To this solution was added 10 mL of saturated NH_4Cl solution, then the solution was extracted with CH_2Cl_2 (20 ml×5). The combined organic phase was dried and condensed, the residue was chromotographed to give 2.0 g (81%) of **7**. $[\alpha]_D^{11}$ -96 (*c* 0.65, $CHCl_3$); IR (neat) 2929, 2856, 1737, 1654, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (br s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.61 (m, 1H), 2.50 (dd, *J* = 15.8, 4.9 Hz, 1H), 2.36 (dd, *J* = 15.8, 12.1Hz, 1H), 2.28 (s, 3H), 1.57 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.25 (br s, 14H), 0.87 (t, *J* = 7.0 Hz, 3H); EIMS *m/z* 309 (M^+); HRMS found *m/z* 309.2318 (M^+), $C_{18}H_{31}NO_3$ requires 309.2332..

Dendrobate alkaloid (+)-241D. To a solution of **7** (0.6 g, 1.9 mmol) in 5 mL of ethanol was added 5 mL of 25% NaOH solution. The mixture was heated to reflux and the refluxing was continued for 6 h, then the mixture was cooled to room temperature and 10 mL of saturated NH_4Cl was added. The solution was extracted with CH_2Cl_2 (20 mL × 5), the combined organic phase was dried and condensed, the residue was chromatographed to give the corresponding enone 0.46 g, yield 78%. To a solution of the enone (80 mg, 0.34 mmol) in methanol was added 10 mg of 10% Pd-C, the mixture was

stirred under H_2 (50 atm) at 50 ^oC for 48 h. After the catalyst was filtered off, the filtrate was condensed and the residue was chromotographed to give 74 mg (92%) of (+)-241D. $[\alpha]_D^{11}$ +7.48 (*c* 1.63, $CHCl_3$); IR (neat) 3271, 3182, 2962, 2921,2852 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.67 (m, 1H), 2.70 (m, 1H), 2.55 (m, 1H), 1.98 (m, 2H), 1.41 (m, 2H), 1.27 (br s, 14H), 1.15 (d, *J* = 6.2 Hz, 3H), 1.02 (m, 2H), 0.89 (t, *J* = 7.0 Hz, 3H); EIMS *m/z* 241 (M^+).

(2*S*)-2-(3'-Phenylmethoxypropyl)-6-propyl-4-oxo-1,2,3,4-tetrahydropyridine-5-carboxylic acid ethyl ester 9. To a solution of **8** (4.2 g, 9.2 mmol) in 20 mL of ethanol was added 0.5 g of 10% Pd-C, the mixture was stirred under H_2 (30 atm) at room temperature for 24 h, the catalyst was filtered off, to the filtrate was add 2.5 mL of HOAc, the solution was stirred at room temperature for 5 min, then the solvent was evaporated. To the residue was added 30 mL of benzene, 0.3 mL of HOAc and 1.7 g (10.7 mmol) of ethyl butanoacetate, the mixture was heated to reflux and the reflux was continued for 12 hours. After the mixture was cooled to room temperature, 10 mL of 20% K_2CO_3 solution was added, then the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL × 3). The combined organic phase was dried and condensed, the residue was chromotographed to give enamine. The enamine was dissolved in 20 mL of dry ethanol, to this solution was added sodium 0.6g (26 mmol), the mixture was heated to reflux and the reflux was continued for 12 h. To this solution was added 10 mL of saturated NH_4Cl solution, the solution was extracted with CH_2Cl_2 (20 ml×5), the combined organic phase was dried and condensed, the residue was chromotographed to give 3.2 g (79%) of **9**. $[\alpha]_D^{20}$ -179.0 (*c* 1.02, $CHCl_3$); IR (neat) 3252, 3086, 2962, 2873, 1697, 1617, 1537 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ7.47 (m, 5H),

6.51 (brs, 1H), 4.53 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.56 (m, 3H), 2.48 (m, 3H), 2.25 (m, 1H), 1.75 (m, 4H), 1.45 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H); EIMS *m/z* 359 (M^+); HRMS found *m/z* 359.2094, $C_{21}H_{29}NO_4$ requires 359.2091.

(2*S*, 4*S*, 6*R*)- 2-(3'-Hydroxypropyl)-6-propyl-4-piperidinol 10. To a solution of **9** (1.4 g, 3.9 mmol) in 10 mL of ethanol was added 10 mL of 25% NaOH. The solution was heated to reflux and the refluxing was continued for 6 h. After cooled to room temperature 10 mL of saturate NH_4Cl solution was added to the solution then it was extracted with CH_2Cl_2 (30 mL × 5). The combined organic phase was dried and condensed, the residue was chromatographed to give 0.88 g (79%) of enone. To a solution of the enone (0.8 g, 2.8 mmol) in 10 mL of methanol was added 0.1 g of 10% Pd-C. The mixture was stirred under H_2 (50 atm) at 50 ^oC for 48 h before the catalyst was filtered off. The filtrate was condensed and the residue was chromotographed to 0.5 g (89%) of **10**. $[\alpha]_D^{20}$ -1.6 (*c* 1.2, CH_3OH); IR (neat) 3338, 2920, 2872 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 3.79 (m, 1H), 3.57 (t, *J* = 6.5 Hz, 2H), 3.04 (m, 2H), 2.15 (m, 2H), 1.58 (m, 6H), 1.35 (m, 2H), 1.28 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H); EIMS *m/z* 202 (M^+ + H^+); HRMS for $C_{11}H_{23}NO_2$ requires *m/z* 201.1729 (M^+), found 201.1727.

(2*S*,6*R*)-2-(3'-Hydroxypropyl)-6-propyl-4-piperidinone 11. To a solution of **10** (0.45 g, 2.2 mmol) in 5mL of 1,4-dioxane was added benzyl chloroformate (1.2 g, 7 mmol) and K_2CO_3 (1.1 g, 8 mmol). The mixture was stirred at 50 ^oC for 12 h, and was then filtered through silica gel. The filtrate was concentrated and the residue was purified by chromatograph to give product. The product was dissolved in 5 mL of dry CH_2Cl_2, to this solution was added Dess-Martin oxidant (0.9 g, 2.1 mmol), the mixture was stirred at room temperature for 3 h, then was filtered through silica gel. The filtrated was

condensed and the residue was chromatographed to give ketone. The ketone was dissolved in 5 mL of methanol, to this solution was added 10% Pd-C, the mixture was stirred at room temperature for 1 h, then the catalyst was filtered off, the filtrate was condensed and the residue was chromatographed to give 0.36 g (82%) of **11**; $[\alpha]_D^{25}$ -10.2 (*c* 1.55, $CHCl_3$); IR (neat) 3289, 2959, 2930, 1712 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 3.62 (m, 2H), 3.10 (br s, 1H), 2.85 (m 2H), 2.42 (m, 2H), 2.12 (m, 2H), 1.62 (m, 8H), 0.95 (t, *J* = 7.2 Hz, 3H); EIMS *m/z* 200 ($M^+ + H^+$).